REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims pending in this application be allowed.

Amendments

Claims 1-27 have been canceled without prejudice or disclaimer. Applicants reserve the right to file a continuation application directed to the subject matter of these claims.

Claims 28-41 are newly presented and are supported by the specification and claims as originally filed. Specifically, new Claim 28 recites that Ar^1 is selected from the group consisting of pyrimidinyl, pyridazinyl and pyrazinyl which are optionally substituted with from 1 to 3 substituents selected from alkyl, substituted alkyl, amino, substituted amino, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl and substituted heterocyclic. Support for this amendment is found in Applicants' specification at, for example, the paragraph bridging pages 12 and 13

Claim 28 further recites a phenyl substituent for Ar^2 as found at, for example, page 13, lines 15-16.

Claim 28 further recites that R^1 is hydrogen or alkyl which were included in the original Markush group found in Claim 1.

Claim 28 further recites that X is hydroxy, alkoxy or substituted alkoxy; all of which were included in the original Markush group found in Claim 1.

Claim 28 further recites a variably substituted pyrid-2-one (Y = CH)/pyrimid-6-one (Y = N) (formula Ia)[1] or an N-substituted pyrid-2-one (Y = CH)/N-substituted pyrimid-6-one (Y = N) (formula Ib)[2].

Support for the variably substituted pyrid-2-one (Y = CH)/pyrimid-6-one (Y = N) (formula Ia) is found in Applicants' specification at, for example, page 9, lines 25-26. Support for the recitation of $(R)_q$ is found in Applicants' specification at, for example, page 9, lines 25-29.

Support for the N-substituted pyrid-2-one (Y = CH)/pyrimid-6-one (Y = N) (formula Ib) is found in Applicants' specification at, for example, page 11, line 17. Support for the recitation of $(R)_q$ is found in Applicants' specification at, for example, page 11, lines 17-20.

Claims 29, 30 and 31 correspond to new Claim 28 with the exception that they are specifically directed to individual Ar^1 groups.

Claim 31 recites that R^1 is hydrogen as found at page 13, line 19.

Claim 32 recites that Y is CH which corresponds to the pyridones found, for example, in Table I found at pages 21-25 as well as at page 9, lines 25-26, and page 11, line 17.

Claim 33 recites that Y is nitrogen which corresponds to the pyrimidones found, for example, in the table at page 22 as well as at page 9, line 26, and page 11, line 17.

Claims 34 and 35 recite that X is hydroxyl which is supported by Applicants' specification at, for example, page 13, line 19.

Claims 36 and 38 recite that *q* is zero which is supported by Applicants' specification at, for example, page page 9, lines 25-29.

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1 Variable substitution is off any carbon atom capable of substitution from the phenyl ring.

2 Substitution from the phenyl ring is to the nitrogen atom alpha to the carbonyl.

Claims 36 and 39 recite that *q* is one and that R is alkoxy which recitation is supported by Applicants' specification at, for example, Table I at pages 21-25.

Claim 40 corresponds to previously presented Claim 20 with the exception that the disease treated is an inflammatory disease as recited at page 88, lines 5-8.

Claim 41 corresponds to previously presented Claim 21.

Applicants note that the above claims are submitted solely for the purpose of expediting allowance of subject matter which is apparently allowable. No new matter has been entered by these amendments and, accordingly, entry of these amendments is earnestly solicited.

For the convenience of the Office, a copy of the now pending claims is attached.

Claim Status

Previously presented Claims 1-27 were subject to a 16 way restriction requirement as found in the Office Action mailed on June 30, 2003 (paper no. 11).

In response to this restriction requirement, Applicants elected, with traverse, Group I which was defined to include Ar^1 as pyrimidyl; B (or C) is pyridone or pyrimidone; Ar^2 is aryl. This group was recited to include compounds of formula (Ia) or (Ib) with the recited limitations as well as the compounds of formula (IIa) or (IIc).

In the present Office Action, this restriction requirement was repeated and made final.

In response to the finality of this restriction requirement, Applicants have canceled Claims 1-27 and inserted Claims 28-41 in place thereof.

Applicants have retained certain of the subject matter of the non-elected inventions in Claim 28 (and other claims). For the purposes of continuity, Applicants submit that of the newly presented claims, Claims 28, 29, and 31-41 read on elected Group I and that Claims 29-30 read

on non-elected groups and, accordingly, for the purpose of this restriction requirement, would be withdrawn from consideration.

Cancellation of claims herein is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. With respect to all cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and, moreover, have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

In view of the above, Claims 28-41 are now in this application.

Restriction Requirement

The finality of the restriction requirement as found in the Office Action as it applied to previously presented Claim 1 is again traversed. For the record, previously presented Claim 1 was restricted into 16 separate groups by the USPTO in the Office Action of June 30, 2003 (paper no. 11). This restriction of Claim 1 was achieved by restricting three separately defined Markush groups into subgroups or individual species. In their response of September 2, 2003, Applicants traversed this restriction requirement for the reasons set forth in detail therein.

Notwithstanding the finality of the restriction requirement, applicants maintain their traversal because it inappropriately restricts Claim 1 into 16 groups. As noted in *In re Weber,* 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334, a refusal to examine what Applicants construe as their invention constitutes a rejection -- not a restriction requirement. Such a rejection is properly cast as a lack of unity of invention. *In re Harnish,* 631 F.2d 716, 206 USPQ 300 (CCPA 1980).

For the purposes of this traversal and for any subsequent appeal, this restriction requirement will be addressed herein in the proper legal context of an improper Markush rejection and this rejection is traversed.

As to any lack of unity of invention rejection, such a rejection is proper only if the claim subject matter lacks a common structural element and a shared common function. *In re Harnish, supra.* With that standard in mind, all of the now presented claims meet these unity of invention criteria.

Specifically, all of the claimed compounds are phenylalanine derivatives each containing a diazoheteroaryl substituent at the amino group of the phenylalanine. Accordingly, all of the claimed compounds share a common structural feature.

Additionally, all of the claimed compounds are VLA-4 antagonists if, for no other reason, then the claims recite that the compounds of Formula I have a binding affinity to VLA-4 as expressed by an IC_{50} of about 15 μM or less. Accordingly, all of the compounds share a common utility.

In view of the above, the now presented claims possess unity of invention and, the rejection of Claim 1, posed as a restriction requirement, is improper. Withdrawal of this rejection is requested.

Examination of all of the now presented claims is deemed appropriate and is requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-3, 6-14 and 17-27 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation and use of compounds having pyridone, pyrimidone, thiadiazole, pyridazine, pyrimidine, or pyrazine, allegedly does not reasonable provide enablement for compounds having other heteroaryl groups [defined for Ar^1, Ar^2, B or C]. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants submit that this rejection has been obviated by virtue of now presented Claim 28 which is directed to Ar^1 groups which are pyridazine, pyrimidine, or pyrazine groups; to Ar^2 which is phenyl; and to B and C which are pyridone and pyrimidone groups.

Withdrawal of this rejection is earnestly solicited.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 20 and 22-25 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabled for a method of treating asthma and allograft rejection, allegedly does not reasonably provide enablement for other diseases that are allegedly mediated by VLA-4 (including those have not been discovered). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In response, now presented Claim 41 recites treatment of an inflammatory disease mediated by VLA-4. Applicants submit that the recitation that the disease is an inflammatory disease obviates this rejection. Specifically, it is well established law that the onus is upon the USPTO to establish lack of enablement and such requires that the Office proffer reasoned evidence as to why the claims are not enabled. Mere allegations of non-enablement are insufficient.

In the present case, no reasoned evidence has been proffered as to why the claims are not enabled other than the allegation that prior art drugs directed to one indication are not suitable for other indications. However, such "evidence" does not address the underlying issue here. That is, the art has recognized that VLA-4/VCAM-1 interaction is a seminal immunological event in the initiation of an inflammatory episode, regardless of its underlying etiology. Applicants have presented many art recognized journal references in the State of the Art section of the application which have established this relationship. The "evidence" presented in the Office Action neither addresses nor contradicts this. Accordingly, Applicants maintain that the "evidence" provided is not reasoned evidence as required by the USPTO to establish non-enablement.

Withdrawal of this rejection is earnestly solicited.

CONCLUSION

Applicants submit that this application is now in condition for allowance. A Notice to that effect is earnestly solicited. In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 50-2859 referencing docket no. 428372001600. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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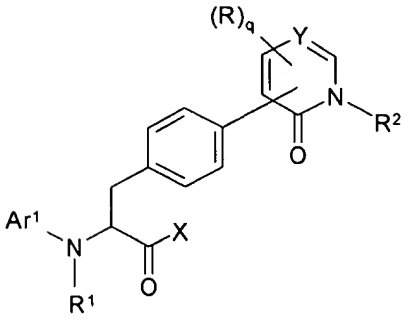
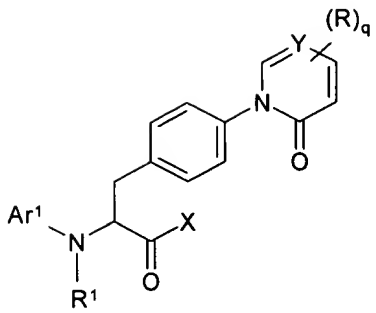
Date: February 18, 2004

PENDING CLAIMS

28. A compound (Ia) or (Ib):



(Ia)



(Ib)

wherein:

Ar^1 is selected from the group consisting of pyrimidinyl, pyridazinyl, and pyrazinyl wherein Ar^1 is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, amino, substituted amino, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

R is selected from the group consisting of alkyl, alkoxy, halo, and mono- and dialkyl-amino;

q is an integer from 0 to 2;

R^1 is selected from the group consisting of hydrogen and alkyl;

Y is CH or N;

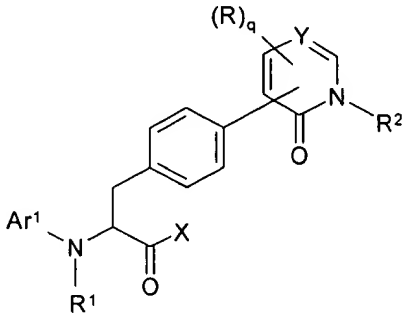
R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl;

X is selected from the group consisting of hydroxyl, alkoxy and substituted alkoxy;

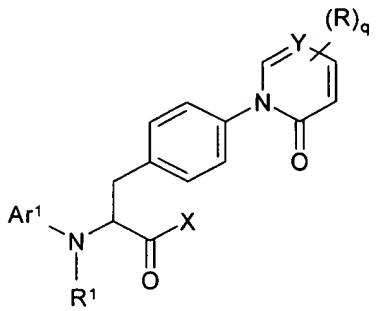
and enantiomers, diasteromers or pharmaceutically acceptable salts thereof;

and further wherein the compound of Formula I has a binding affinity to VLA-4 as expressed by an IC_{50} of about 15μM or less.

29. A compound (Ia) or (Ib):



(Ia)



(Ib)

wherein:

Ar^1 is pyrimidinyl which is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, amino, substituted amino, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

R is selected from the group consisting of alkyl, alkoxy, halo, and mono- and dialkyl-amino;

q is an integer from 0 to 2;

R^1 is selected from the group consisting of hydrogen and alkyl;

Y is CH or N;

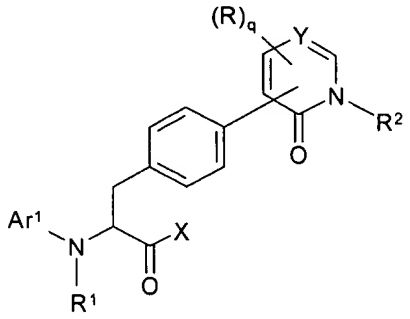
R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl;

X is selected from the group consisting of hydroxyl, alkoxy and substituted alkoxy;

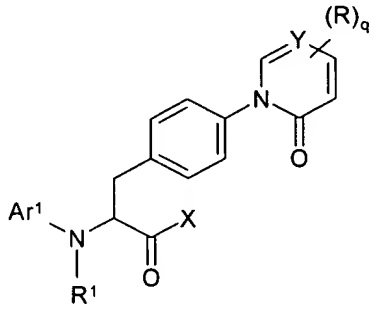
and enantiomers, diasteromers or pharmaceutically acceptable salts thereof;

and further wherein the compound of Formula I has a binding affinity to VLA-4 as expressed by an IC_{50} of about 15μM or less.

30. A compound (Ia) or (Ib):



(Ia)



(Ib)

wherein:

Ar^1 is pyridazinyl which is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, amino, substituted amino, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl,heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

R is selected from the group consisting of alkyl, alkoxy, halo, and mono- and dialkyl-amino;

q is an integer from 0 to 2;

R^1 is selected from the group consisting of hydrogen and alkyl;

Y is CH or N;

R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl;

X is selected from the group consisting of hydroxyl, alkoxy and substituted alkoxy;

and enantiomers, diasteromers or pharmaceutically acceptable salts thereof;

and further wherein the compound of Formula I has a binding affinity to VLA-4 as expressed by an IC_{50} of about 15μM or less.

31. The compound according to any of Claims 28, 29 or 30 wherein R^1 is hydrogen.

32. The compound according to Claim 31 wherein Y is CH.

33. The compound according to Claim 31 wherein Y is N.

34. The compound according to Claim 32 wherein X is hydroxy.

35. The compound according to Claim 33 wherein X is hydroxy.

36. The compound according to Claim 34 wherein *q* is zero.

37. The compound according to Claim 34 wherein *q* is one and R is alkoxy.

38. The compound according to Claim 34 wherein *q* is zero.

39. The compound according to Claim 34 wherein *q* is one and R is alkoxy.

40. A method for treating an inflammatory disease mediated by VLA-4 in a patient, which method comprises administering a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 28-39.

41. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 28-39.